# DEVELOPMENT OF NEW SYNTHETIC TOOLS FOR THE PREPARATION OF BIOLOGICALLY ACTIVE MOLECULES

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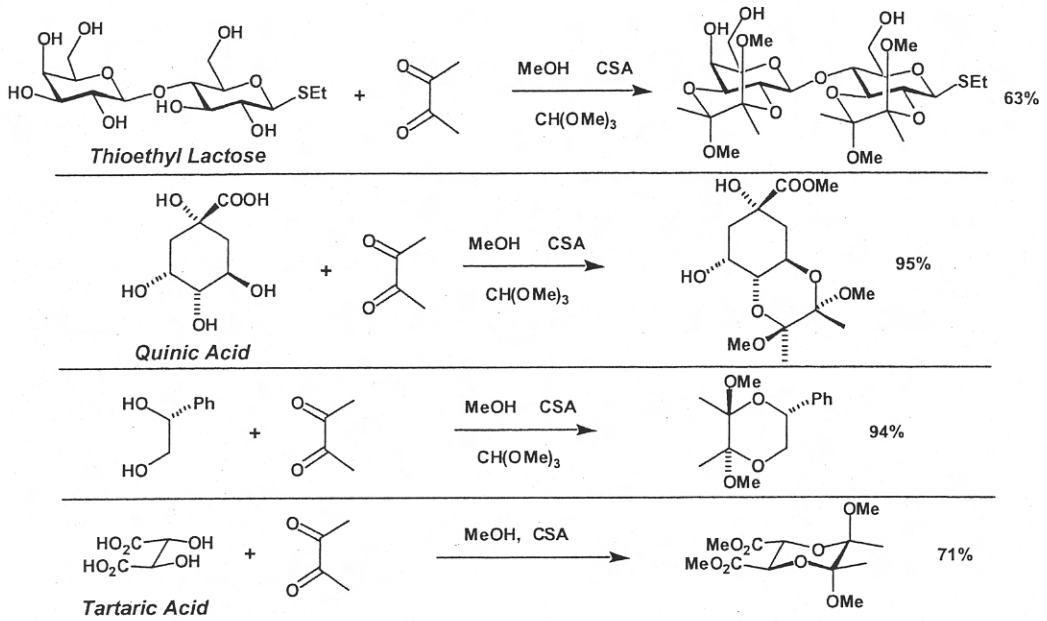
## 1. Introduction

The synthesis of organic compounds, especially biologically active molecules, is a very complex task involving many important decision making steps. These decisions are especially important at the synthesis planning stage where issues of regio-, chemo- and stereo-control and the knowledge of mechanisms and functional group compatibility are paramount. Furthermore, if the plan uses more creative and innovative approaches rather than a more logistic and strategic approach even more careful understanding and preparation is required. Even given a workable plan there are several further phases where key decisions need to be made. For example the selection of the reaction conditions to effect a specific transformation involves specific knowledge or extensive optimisation of a vast range of reagents, safety factors, solvents and temperatures that can be quite a phenomenal exercise. This part of the process also makes use of considerable operator experience especially when scale and cost issues are important.

Next the reaction processes need to be monitored so as to determine the reaction time and whether exotherms occur. This requires further expertise of analytical techniques. Finally, if all has gone well, the last phase of work-up to produce a clean product can be the most time-consuming and skilled part of the operation. Here laboratory skills involving distillation, crystallisation, liquid extraction, filtration and chromatography are vital to the success. Indeed there is a real art as well as a craft to the process of molecular assembly.
As chemists we are constantly challenged by complex molecules especially those that show important biological properties such as natural products. Carbohydrates and oligo-saccharides for example present a particularly difficult challenge as these necessitate extensive steps involving specific functional group protection and anomeric group activation in order to effect their assembly. Moreover, the range and structural types involved and the opportunities for branching further complicate the problem.
We have therefore devised alternative solutions especially for the selective protection of equatorial diols using 1,2-diacetals (Scheme 1) [1].

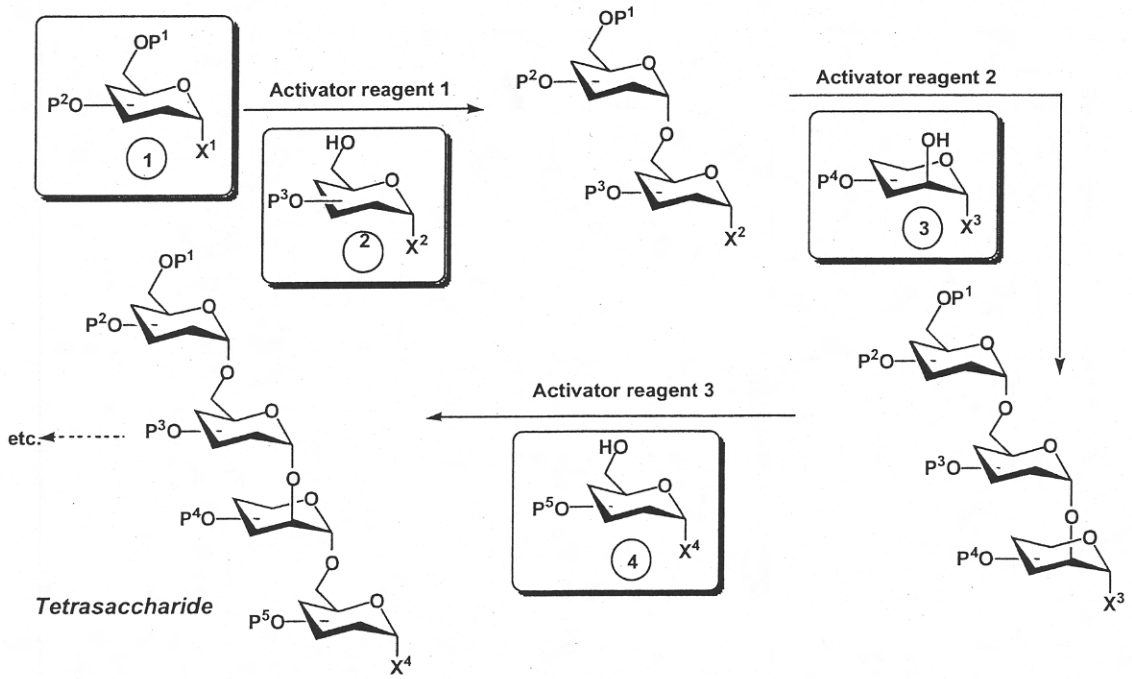


*M.P. Schneider (ed.), Chemical Probes in Biology,* 235–244.



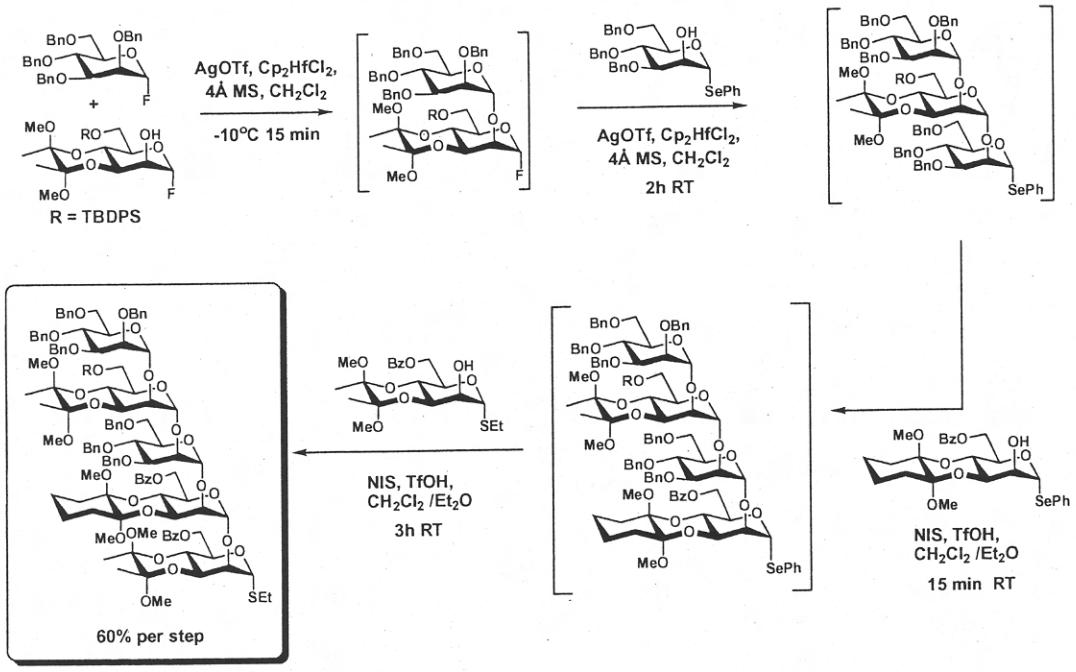

*Scheme 1.* Butane-2,3-diacetal (BDA ) Protection.

These novel protecting systems further tune the reactivity of the building blocks in glycosidic coupling reactions to make oligosaccharides in a single reaction pot from monomer starting materials. To understand this concept we can envisage the coupling of components in a linear fashion, requiring anomeric leaving groups compatible with matched activators to facilitate specific coupling with a second saccharide containing free hydroxyl groups that then leads to a disaccharide (Scheme 2) [2].

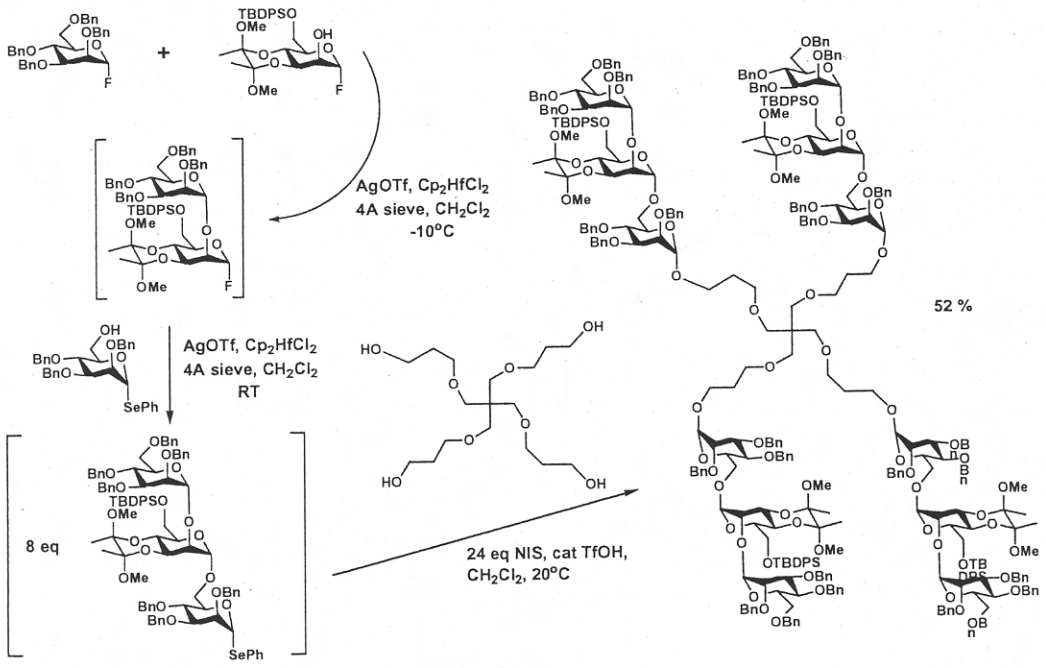



*Scheme 2.* One-pot Oligosaccharide Assembly, Linear Coupling of Monomer Building Blocks for Carbohydrate Library Synthesis.

This component also contains orthogonal anomeric leaving groups which maybe selectively further activated and then coupled with a third component to afford trisaccharides. The process can in principle be repeated to make even larger systems. Furthermore, given the reaction tuning that arises by making fused 1,2-diacetals as protecting groups even larger oligomers can be made in single reaction pots (Scheme 3,4) [3].

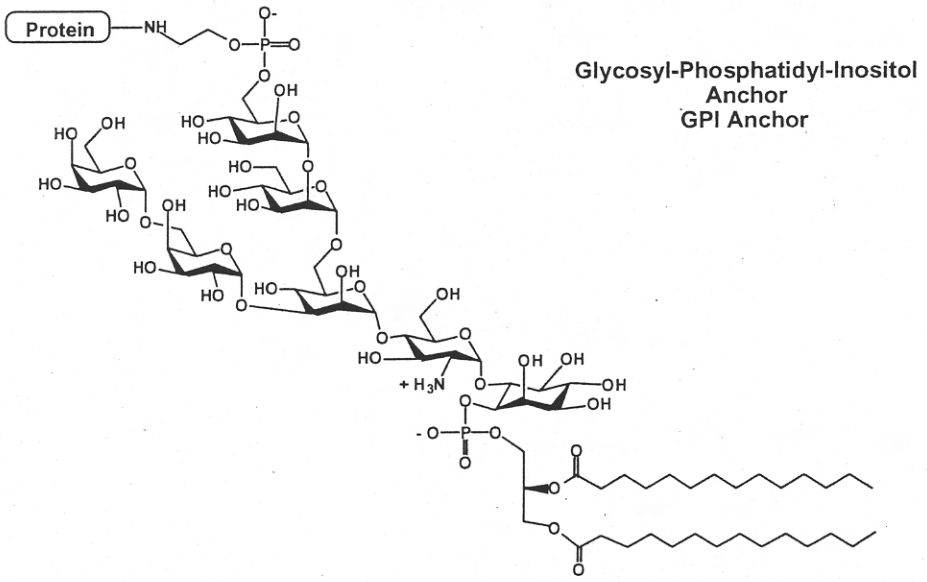



*Scheme 3.* One-Pot Linear Pentasaccharide Synthesis.



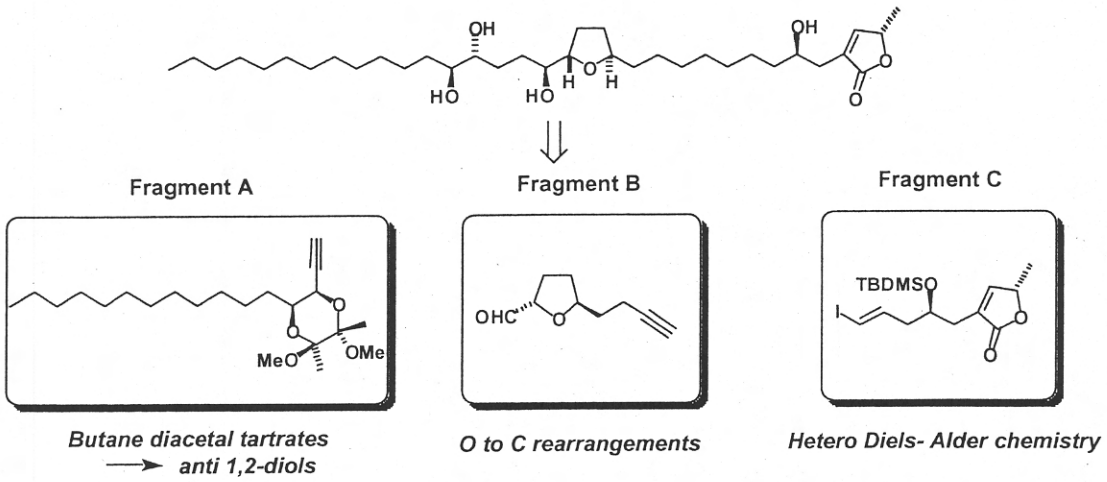

*Scheme 4.* One Pot Preparation of a Dodecasaccharide-Dendrimer.

We have also sought to use these protocols to prepare more elaborate systems such as the Glycosyl-Phosphatidyl-Inositol (GPI) anchor found in the variant surface glycoprotein of *Trypanosoma brucei* (Scheme 5) [4]. This synthesis has been published consequently we will not review the details of this work here [5]. Nevertheless this synthesis very effectively demonstrates the power of using butane-1,2-diacetals as selective protecting groups enabling advanced one-pot oligosaccharide assembly.



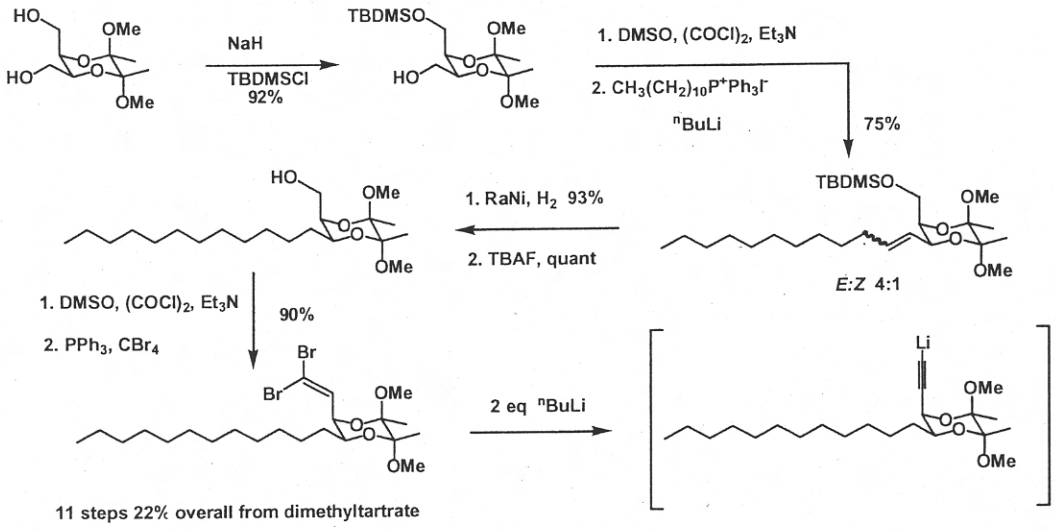

*Scheme 5.* Variant Surface Glycoprotein of *Trypanosoma brucei.*

While the use of 1,2-diacetals was very useful in the carbohydrate area they also turn out to be more generically acceptable in many other complex natural product syntheses. We can illustrate this by examining the preparation of the antitumour agent Muricatetrocin C [6] the plan for which is shown in scheme 6 [7].



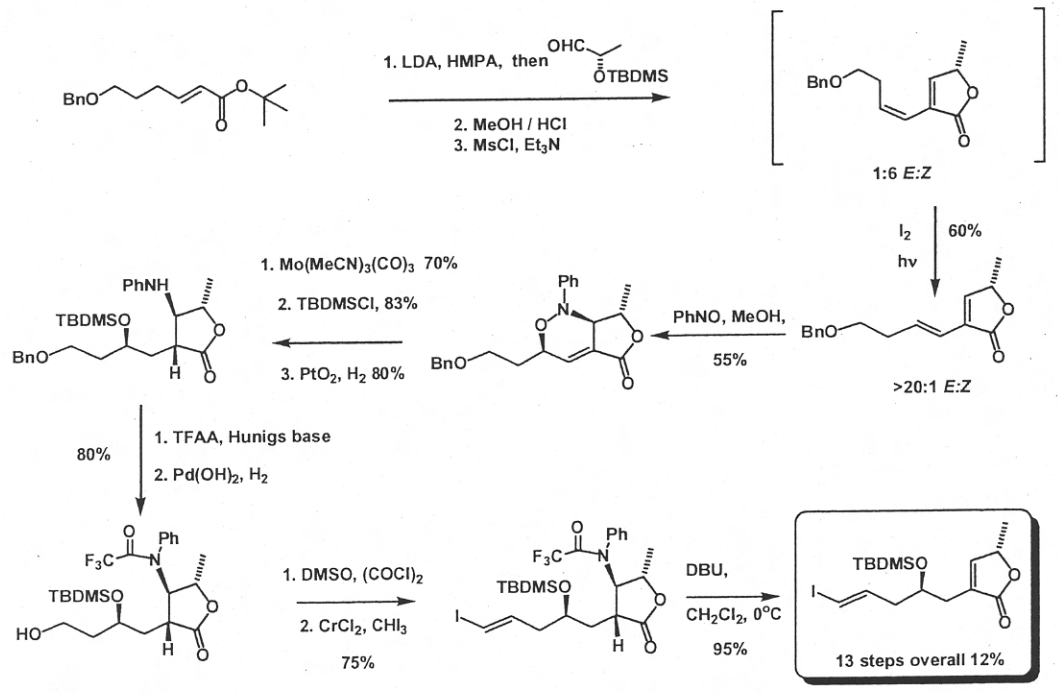

*Scheme 6.* Muricatetrocin C Synthesis.

The synthesis requires the preparation of three fragments, A, B and C which will then be coupled to afford the natural product itself [7]. The key fragment A is prepared from a butan-1,2-diol protected tetraol building block itself prepared from tartaric acid (Scheme 7) [8]. This again illustrates the important use of the BDA units to selectively control substitution patterns and hence facilitate later reactions.

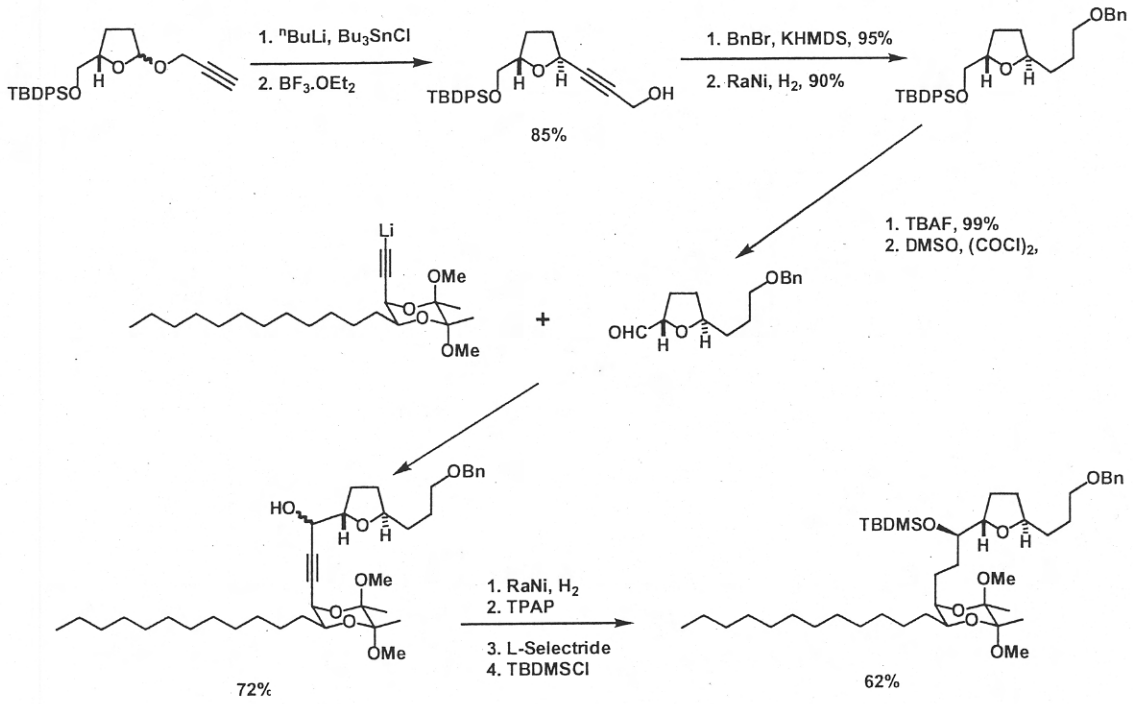



*Scheme 7.* Muricatetrocin C; Synthesis of Fragment A.

The preparation of the other fragment, C is shown in scheme 8 and the further coupling with the fragment B given in Scheme 9.

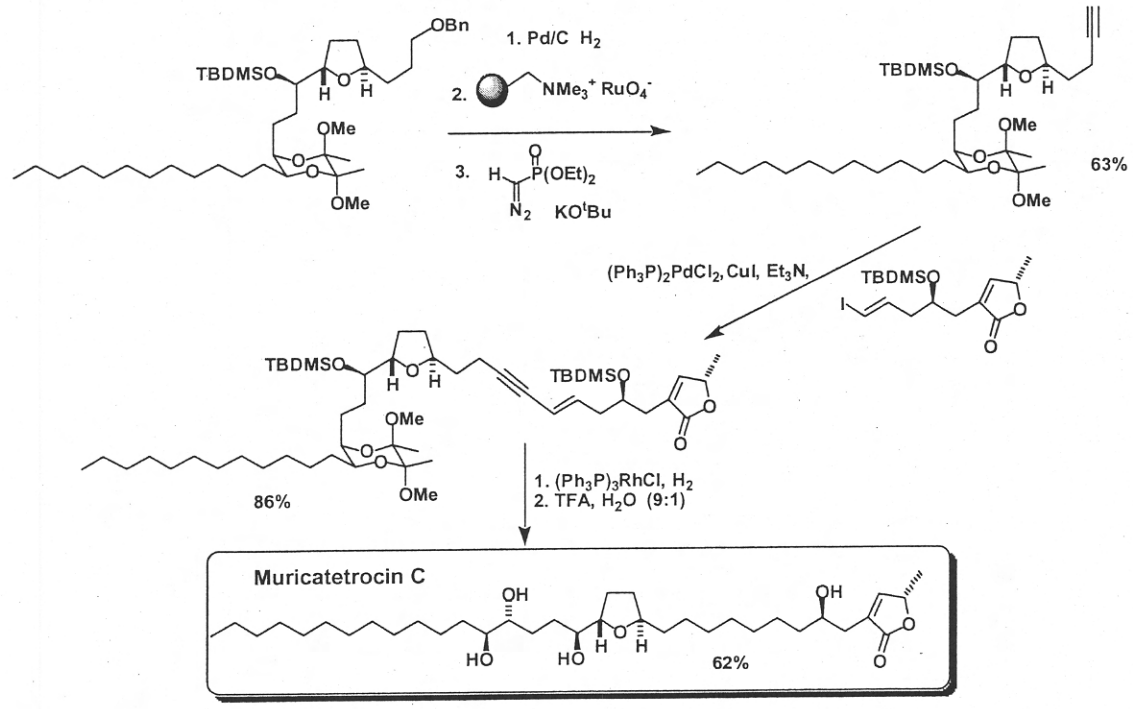



*Scheme 8.* Muricatetrocin C; Synthesis of Fragment C.




*Scheme 9.* Muricatetrocin C; Fragment B Synthesis and Coupling.

The final coupling and conversion to the natural product follows a late stage Sonagashira coupling reaction (Scheme 10).



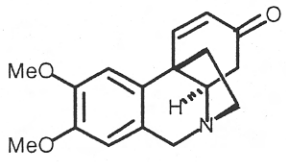

*Scheme 10.* Muricatetrocin C; The Final Coupling Strategy.

This last scheme also illustrates the use of an immobilised oxidant to effect oxidation of an intermediate alcohol to an aldehyde. What is important in this process is that not only is the reaction catalytic, the spent reagent can be isolated by simple filtration and may then be recycled and reused [9]. In fact the idea of using immobilised reagents in multi-step organic synthesis, especially for the synthesis of natural products is very attractive. A conventional synthetic approach usually requires extensive chromatography to obtain pure products. This is both wasteful in material, solvents and in silica gel itself. Even if distillation or crystallisation of products is possible these are advanced techniques that are still extremely time-consuming to perform.

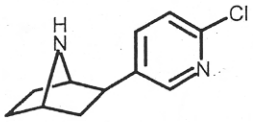
These days where we require cleaner chemistry and the ability to obtain vast chemical compound libraries for biological evaluation these manpower intensive operations are unacceptable especially if we wish to use more automation and robotic systems. For these reasons and in order to advance and develop the tool-box for organic synthesis, we have examined alternative strategies that allow multi-step synthesis to be performed using only immobilised reagents and scavengers to effect all the synthesis steps [10].

Some of the key advantages of this methodology include: the ability monitor reactions with traditional analytical methods, the selection of a wide range of organic reactions, convergent/divergent and linear synthetic strategies are possible providing maximum structure diversity and no polymer attachment/cleavage steps are necessary. These concepts also allow for scale up of reactions using procedures that can be readily adapted to automation, to provide significant quantities of both intermediates and final products cleanly without the need for conventional work-up sequences.

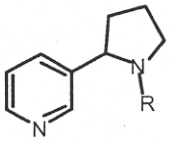
The advantages of supported reagents for orchestrated multi-step organic synthesis has been previously demonstrated in the total synthesis of the natural products, (±)-oxomaritidine [11], (±)-epibatidine [12] and the alkaloids nicotine and nornicotine [13] (Figure 1). In addition we have carried out the synthesis of a number of more advanced molecules as shown in scheme 11, 12 and 13 below.




(±)-oxomaritidine



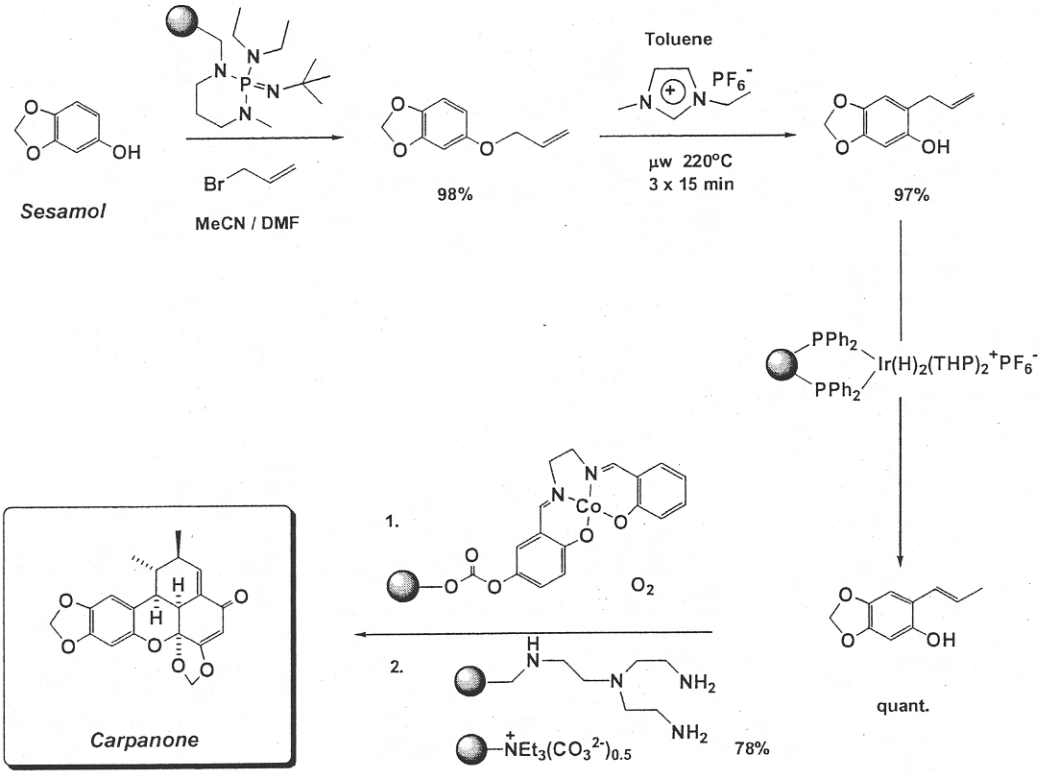

(±)-epibatidine



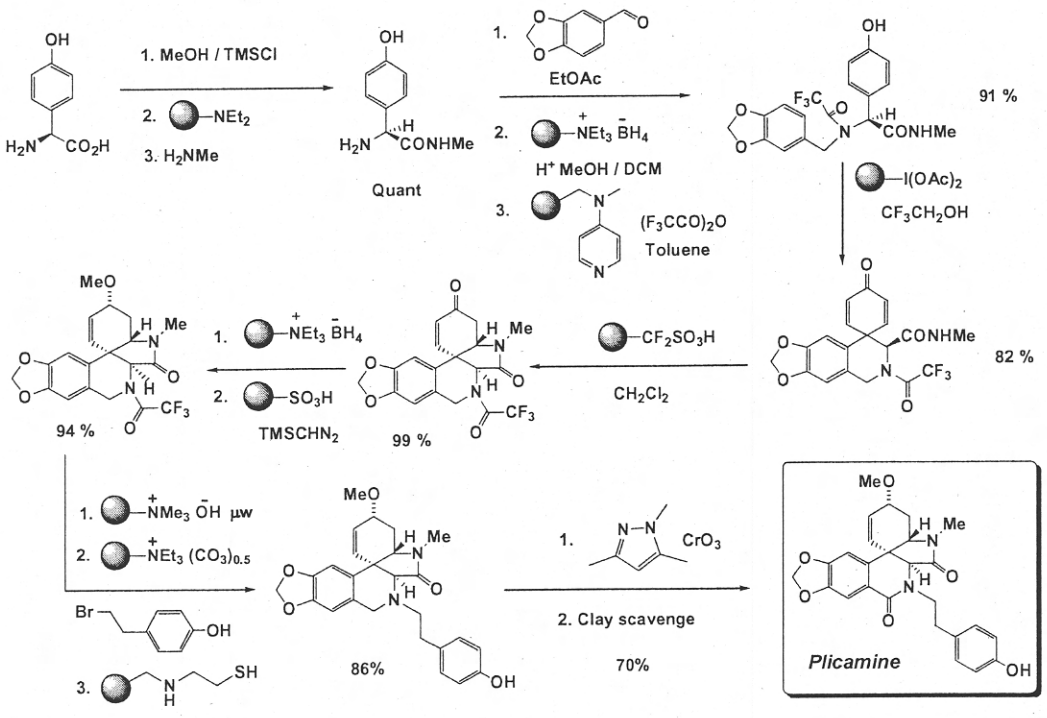

R = H; nornicotine
R = Me; nicotine

*Figure 1.* Natural Products Synthesised Using Immobilised Reagents.

The natural product (±)-carpanone [14] possess an attractive and relatively complex architecture that can be rapidly assembled from the basic starting material, sesamol [15]. Using a sequence of immobilised reagents and catalysts a clean and rapidly optimised synthesis was performed. The final product was isolated in 66% overall yield and in greater than 90% purity following a rapid scavenging sequence in order to remove any trace amounts of by-products or unreacted monomer starting material.



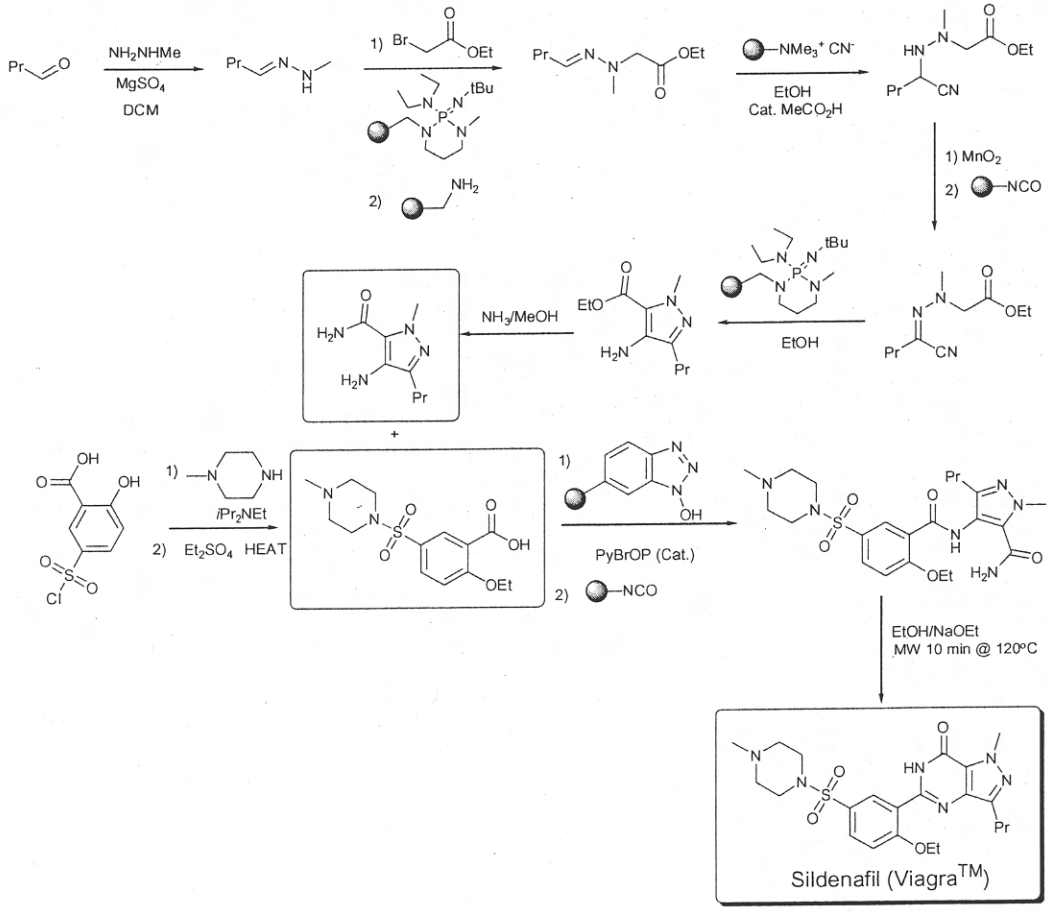

*Scheme 11.* Synthesis of Carpanone Using Immobilised Reagents.




*Scheme 12.* Synthesis of the natural product (+)-Plicamine.

Applying the same methodology, the synthesis of a recently isolated amaryllidaceae alkaloid (+)-plicamine [16] was conducted utilising twelve different immobilised reagent systems [17]. This approach highlights the relatively advanced structures that can be easily accessed using this technological approach. The synthesis starts from optically pure 4-hydroxyphenyl glycine, the stereochemistry of this amino acid is used to control all the subsequent stereo defining steps, therefore importantly permitting access to the unnatural enantiomer form of plicamine by starting from the alternatively configured amino acid. In addition to generating the target compound in both enantiomeric forms this approach permitted the parallel synthesis and generation of significant pools of intermediates for use in the construction of many unnatural analogues and natural product like compounds.

Our interest in demonstrating the applicability of the polymer-supported reagents to practical situations has also cumulated in the synthesis of the important pharmaceutical drug molecule Sildenafil (Viagra$^{TM}$) (Scheme 13). Our synthesis [18] of this molecule shows one of the first examples of using the supported reagents in both a sequential and convergent fashion. This synthesis also demonstrates the potential of these reagents in the development process of new compounds.




*Scheme 13.* The Synthetic Preparation of Sildenafil.

We believe that these methods will find many very important applications in the future not just for natural product synthesis but also for diversity orientated synthesis programmes and for new catalyst discovery. Likewise we can envisage their application in process optimisation and new reagent discovery and the possibility of inventing new reactions. We are already seeing these reagent systems being integrated into many synthetic programmes across all areas of chemistry from the early design and development experiments to large-scale manufacturing. Undoubtedly this is a trend that will certainly increase with time.

## 2. References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